

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:)	Art Unit: 1625
Jacob WESTMAN et al)	Examiner: Niloofar RAHMANI
Appln. No.: 10/590,054)	Washington, D.C.
Filed: March 22, 2005)	Confirmation No. 5605
371(c) dated: August 21, 2006)	
For: AZABICYCLOOCTAN-3-ONE)	ATTY.'S DOCKET: WESTMAN=3
DERIVATIVES AND USE...)	

DECLARATION UNDER 37 CFR 1.132

I, Nina Mohell, hereby solemnly declare as follows.

I was awarded a PhD degree in Animal Physiology from the University of Stockholm, Sweden in 1985, and three years later became an Associate Professor. In 2000, I was appointed Adjunct Professor in Molecular Pharmacology at the Faculty of Medicine, University of Uppsala, Sweden. Attached is a shortened form of my CV which is made a part hereof.

I am not a co-inventor of the above-identified U.S. patent application, but I am familiar with it, having read such U.S. patent application and the Official Letter of the Examiner dated June 23, 2008.

In the Official letter, the U.S. Examiner indicates that "Applicants provide some examples of tested compounds and WST-1 assay" but "provide no guidance for how WST-1 assay could treat any and all known or unknown diseases". The Examiner furthermore indicates that "There are no examples in

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the instant specification showing that the instant compounds can treat any diseases". The Examiner furthermore indicates that "one of ordinary skill in the art, even with high level of skill, is unable to use the instant compounds without undue experimentation".

Based on my knowledge and expertise, I disagree with the conclusion of the U.S. Examiner.

WST-1 cell proliferation/survival assay is a well-established test that is frequently used to measure cell proliferation/survival. In the present application, WST-1 assay is used to measure proliferation of human tumor cells carrying p53 mutation, measured after treatment with inventive compounds, compared to after treatment with vehicle only. The IC50 values of the various inventive compounds found in this test clearly show that the inventive compounds have an anti-hyperproliferative activity. The application also describes a further test (FACS analysis) wherein the effect of the compounds of the invention on apoptosis of human tumor cells carrying p53 mutation is shown, cf. the description paragraph [0100] and results shown in bar charts of the Figure of the application. Based on these findings, in combination with the scientific background as described under "Background of the invention" the skilled person is able to draw the conclusion

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that the inventive compounds are useful for the treatment of hyperproliferative disorders, notably cancer.

Thus, the application provides results from two different relevant in vitro tests to show that the compounds of the invention have an effect on the proliferation and/or viability of human tumor cells. I believe that these tests correlate well with the claimed method of the present invention. I also believe that a person skilled in the art would accept the tests described in the invention as reasonably correlating to a hyperproliferative condition. I therefore believe that the description of the instant application gives the skilled person adequate information to carry out the invention.

Nevertheless, compounds of the invention of the above-identified U.S. application have been studied in various experiments, both in vitro and in vivo, with promising results, I have been involved with these studies, and can confirm their accuracy, the procedures and results of which are set forth below.

In vitro studies

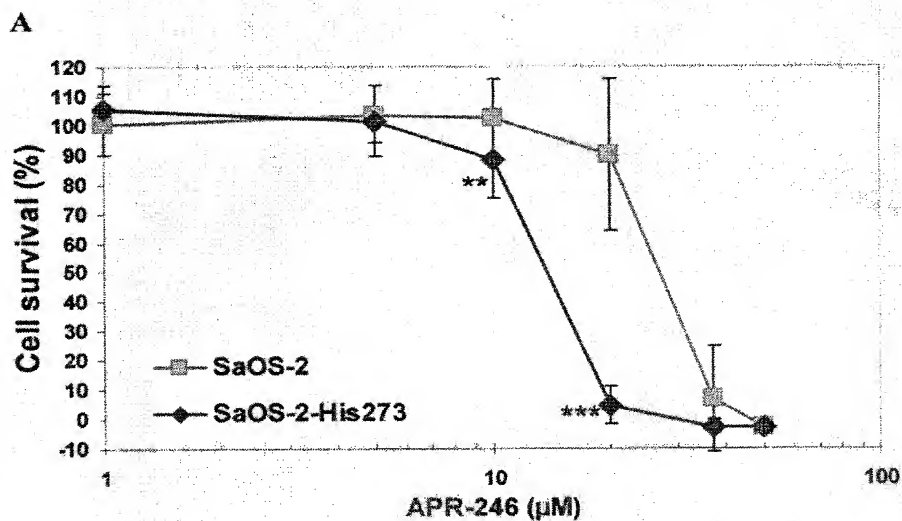
In vitro studies indicate that the inventive compounds have a pronounced inhibitory effect on cancer cell survival and that the activity pattern of the inventive

compounds is different from that of many common
chemotherapeutic drugs.

**1. The inventive compounds inhibit cell viability in
osteosarcoma cells**

In vitro studies demonstrated that compounds of the
invention potently inhibit cell viability and induce apoptosis
in osteosarcoma cells with mutant p53 (SaOS-2-His273) as well
as in null p53 (SaOS-2) osteosarcoma cells, being more potent
in osteosarcoma cells with mutant p53. Results in respect of
two representative compounds of the invention, APR-246 and
APR-305 are shown in Figs.1 (APR-246) and 2 (APR-305).

Fig 1.



B

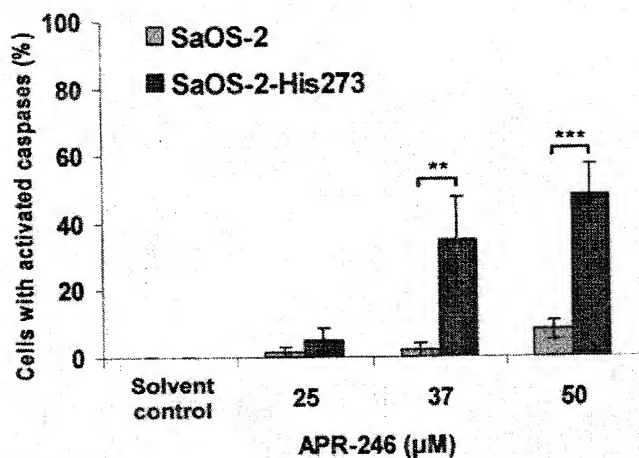
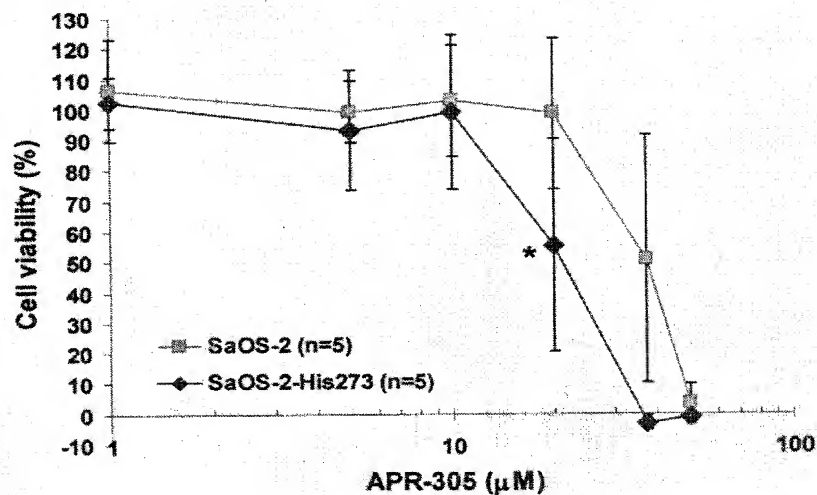


Figure 1. A) Dose-response inhibition curves of APR-246 in SaOS-2 and SaOS-2-His273 cells. Various concentrations of APR-246 were tested in WST-1 proliferation/viability assay. The IC_{50} of APR-246 was 14.5 μM in SaOS-2-His273 cells and 28 μM in SaOS-2 cells (mean \pm SD, n=16). **B)** Effect of APR-246 on apoptosis induction in SaOS-2 and SaOS-2-His273 cells. Various concentrations of APR-246 were tested in FLICA apoptosis assay (mean \pm SD, n=5).

Fig 2.

A



B

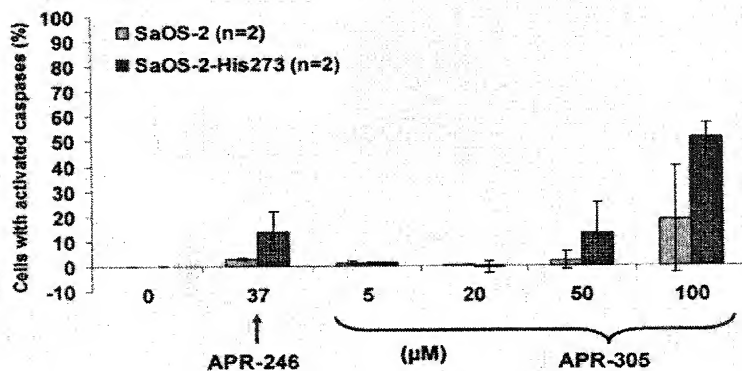


Figure 2. A) Dose-response inhibition curves of APR-305 in SaOS-2 and SaOS-2-His273 cells. Various concentrations of APR-305 were tested in WST-1 proliferation/viability assay. The IC_{50} of APR-305 was 22 μ M in SaOS-2-His273 cells and 38 μ M in SaOS-2 cells (mean \pm SD, n=5). B) Effect of APR-305 on apoptosis induction in SaOS-2 and SaOS-2-His273 cells. Various concentrations of APR-305 were tested in FLICA apoptosis assay (mean \pm SD, n=2). APR-246 was used as a positive control.

2. The inventive compounds reduce cell viability in various cancer cell lines with different p53 status

Compounds of the invention were further tested in vitro in various cancer cell lines of different p53 status. For each cell line the IC₅₀ value was calculated. It was found that compounds of the invention reduce cell viability in various cancer cell lines of different p53 status. In **Table 1**, results for one representative compound of the invention, viz. APR-246, are shown, and in **Table 2** results for three representative compounds of the invention, viz. APR-246, APR-305 and APR-310, in various cancer cell lines are shown. All compounds reduced cell viability in various cancer cell lines with different p53 status.

Table 1. Effect of APR-246 on cell viability in various cancer cell lines (WST-1 assay).

Type of cancer	Cell type	p53 status ¹	IC ₅₀ (μM) APR-246
Osteosarcoma	SaOS-2	null	27±5 (n=33)
Osteosarcoma	SaOS-2-His273	mut His273 (exogenous)	14±3 (n=35)
Osteosarcoma	U-2OS	wt	15±4 (n=5)
Breast ductal carcinoma	BT-474	mut Lys285	3±2 (n=2)
Breast adenocarcinoma	MCF-7	wt	15±1 (n=3)
Breast adenocarcinoma	MDA-MB-231	mut Lys280	18±5 (n=6)
Prostate adenocarcinoma	PC3-puro	null	27±3 (n=3)
Prostate	PC3-175	mut His175	23±7 (n=3)

adenocarcinoma		(exogenous)	
Prostate carcinoma	22Rv1	mut Gln331	10±0.6 (n=3)
Colorectal adenocarcinoma	HT-29	mut His273	25±5 (n=6)
Non-small cell lung carcinoma	H1299	null	16±7 (n=6)
Non-small cell lung carcinoma	H1299-His175	mut His175 (exogenous)	14±8 (n=6)
Acute Myelomonocytic Leukaemia	KBM3	mut His273	7±1 (n=6)

The results are shown as mean±SD; the IC₅₀ values are calculated as the average of the IC₅₀ values in the individual experiments 1) Mutation is endogenous if not otherwise stated

Table 2. Effect of APR-246, APR-305 and APR-310 on cell viability in various cancer cell lines (WST-1 assay).

Inventive Compound	SaOS-2 IC ₅₀ ±SD	SaOS-2-His273 IC ₅₀ ±SD	KBM3 IC ₅₀ ±SD
APR-246	24±5 (n=5)	14±1 (n=5)	7±1 (n=2)
APR-305	36±9 (n=5)	21±6 (n=5)	10±1 (n=2)
APR-310	66±9 (n=3)	45±15 (n=5)	not tested

SaOS-2 (p53 null) and SaOS-2-His273 are osteosarcoma cell lines, and KBM3 is an acute myelomonocytic leukemia cell line with a His273 p53 mutation.

3. The activity pattern of the inventive compounds is different from that of many common chemotherapeutic drugs

The pharmacological profile/activity pattern of compounds of the invention was also tested using a panel of

ten different human cancer cell lines representing different disease backgrounds as well as mechanisms of drug resistance. These experiments were performed by the Anticancer Drug Study Group lead by Rolf Larsson at Uppsala University Hospital. The results expressed as IC₅₀ values, show that the compounds of the invention are active against various types of cancer cell lines. In **Table 3**, results of three representative compounds are shown.

Table 3. A panel of human tumor cell lines used in a study performed by the Anticancer Drug Study Group. IC₅₀ values (μM) for APR-246, APR-305 and APR-310 in these cell lines are listed to the right.

Cell line	Origin	Selecting agent	Resistance associated with	APR 246	APR 305	APR 310
CCRF-CEM	Leukemia	-		13	57	40
CEM/VM-1	"	teniposide	topoisomerase II	14	56	36
ACHN	Renal cancer	-	(primary resistance)	35	>100	46
NCI-H69	Small cell lung cancer	-		2.2	7.5	6.6
H69AR	"	doxorubicin	MRP	21	48	40
RPMI 8226/S	Myeloma	-		14	44	42
8226/dox40	"	doxorubicin	Pgp	8.8	40	28
8226/LR5	"	melfhalan	glutathione	43	68	44
U-937 GTB	Lymphoma	-		2.4	9.2	7.6
U-937-vcf	"	vincristin	tubulin	5.9	11	8.8

The inhibitory activity of the inventive compounds in the ten cell lines differed from that of many common chemotherapeutic drugs as shown by low correlation coefficients (<0.4), listed in **Table 4**. Thus, the inventive

compounds seem to have an activity pattern showing a unique profile.

Table 4. Correlation coefficients with five standard chemotherapeutics of different mechanistic classes (Melphalan = alkylating agent; Doxorubicin = anthracyclin, topoisomerase II inhibition and intercalation; Cytarabine = antimetabolite; Topotecan = topoisomerase I inhibitor; Vincristin = tubulin acting).

Reference drug	APR 246	APR 305	APR 310
Melphalan	0,38	0,22	0,25
Doxorubicin	0,36	0,36	0,29
Cytarabine	0,29	0,19	0,22
Topotecan	0,36	0,30	0,32
Vincristin	0,13	0,08	0,03

In vivo studies

Compounds of the invention have been studied not only *in vitro*, but also *in vivo*. Also the *in vivo* studies show that the inventive compounds have a pronounced anti-cancer activity in the following *in vivo* cancer models:

1. In vivo xenograft experiments in mice show that the inventive compounds have a significant anti-cancer effect

A statistically significant anti-cancer effect in *in vivo* xenograft experiments with mutant p53 osteosarcoma cells SaOS-2-His273 (Fig. 3) has been shown for compounds of the invention.

Figure 3 shows the volume of p53 mutant xenograft tumors in SCID mice, treated intravenously with APR-246 or with PBS (the vehicle, control), at a dosage of 100 mg/kg, twice a day, 3-4 days/week. As can be seen, at the end of the treatment period, the mean tumor volume in control animals was more than three times as high as that in animals treated with APR-246. Differences in tumor volumes were analyzed using Mann-Whitney test. A statistically significant anti-cancer effect was found.

Fig 3.

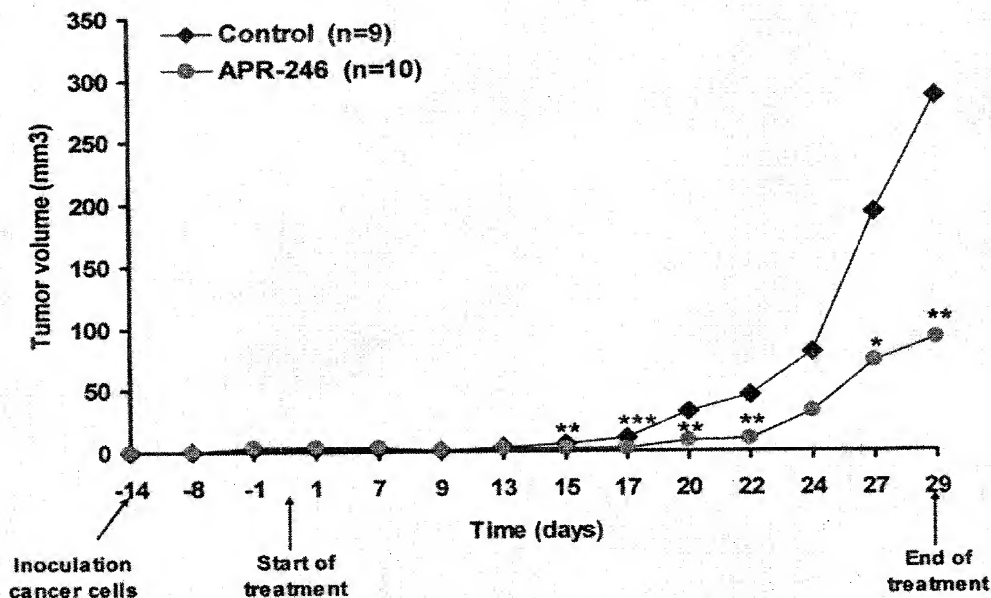


Figure 3. Effect of APR-246, 100 mg/kg, on SaOS-2-His273 xenograft tumors in SCID mice.

2. In vivo experiments with mouse tumors carrying mutant p53
show that the inventive compounds have a significant anti-cancer effect

The effect of APR-246 *in vivo* has also been studied by the research group of Klas Wiman (one of the inventors) in experiments using a mouse sarcoma model (**Figure 4**) and a chemically induced fibrosarcoma model (**Figure 5**). In these models APR-246 showed a statistically significant anti-tumor effect. The results provide additional support for an anti-tumor effect of APR-246 on mutant p53 tumors *in vivo*.

Fig 4.

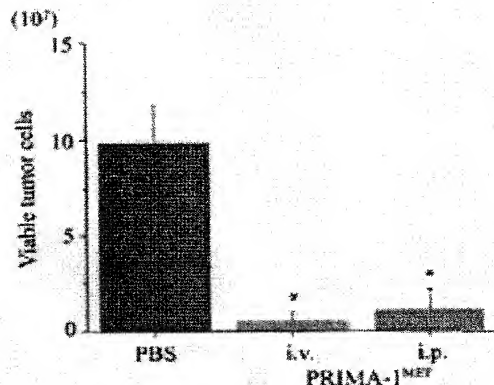


Figure 4. Effect of i.v. or i.p. treatment of APR 246 (PRIMA-1^{MET}), 100 mg/kg, daily, for 10 days, on MC1M mouse sarcoma cells grown as ascites tumors in syngeneic C3H/Hen mice (Zache et al., Cell Oncol. 2008;30(5):411-8). The MC1M cells inoculated in this experiment carry a V213M mutant p53.

Fig 5.

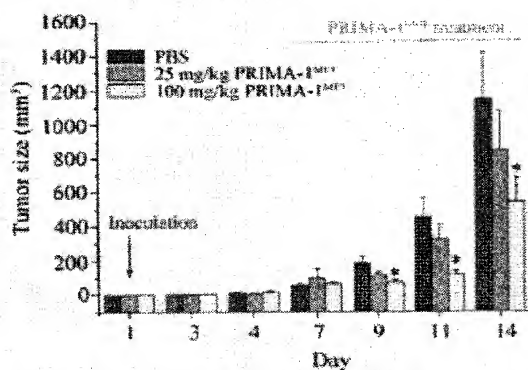


Figure 5. Effect of i.v. treatment of APR 246 (PRIMA-1^{MET}), 25 mg/kg or 100 mg/kg, daily, for 10 days, on MCO4 cells grown as solid subcutaneous tumors in syngeneic Balb/c mice (Zache et

al., Cell Oncol. 2008;30(5):411-8). The MCO4 cell line is derived from a 3-methylcholanthrene-induced mouse fibrosarcoma. The cells express two mutant p53 species, one carrying the G65R and R277I mutations and one carrying the R246L mutation.

3. In vivo experiments using the hollow fiber mouse model with inventive compounds show that inventive compounds have a significant anti-leukemic effect

Experiments have also been performed with APR-246 at Visionar Preclinical AB using the hollow fiber in vivo mouse model (for a short description of the model, cf.

http://dtp.nci.nih.gov/timeline/noflash/milestones/M13_hollow_fiber.htm). As shown in **Figure 6**, at the end of the experiment the net growth of leukemic cells (AML MV-4-11 cells) was about 25% (by number) in mice treated with vehicle only (control). On the other hand, in mice treated with APR-246, the net growth of leukemic cells was about -25% by the end of the experiment, i.e. the number of leukemic cells had effectively decreased. Thus, it was shown that APR-246 has a statistically significant anti-leukemic activity in vivo.

Fig 6.

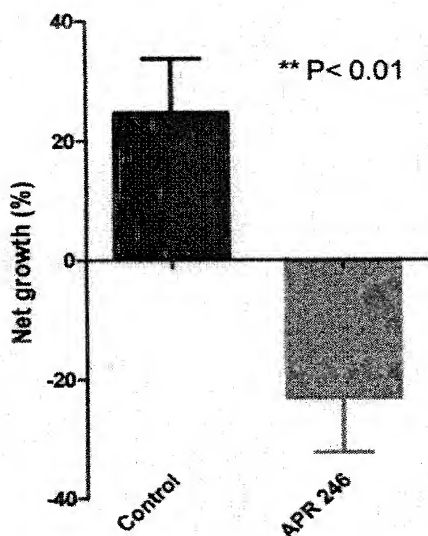


Figure 6. Effect of APR-246 on AML MV-4-11 cells in the hollow fiber *in vivo* model. Data is shown as mean \pm SEM (n=7-8).

4. *In vivo* xenograft experiments with oral administration of inventive compounds to mice show that inventive compounds have a significant anti-cancer effect

Experiments with oral administration of compounds of the invention to SCID mice inoculated with xenografts of p53 osteosarcoma cells have also been performed, with very promising results. **Figure 7** illustrates the effect on SaOS-2-His273 xenograft tumors in SCID mice of oral administration of a representative compound of the invention, viz. APR-305, at a dosage of 200 mg/kg, twice a day, 7 days. The difference in tumor volume growth was analyzed using two tailed unpaired t-

test, unequal variance. A statistically significant anti-cancer effect was found.

Fig 7.

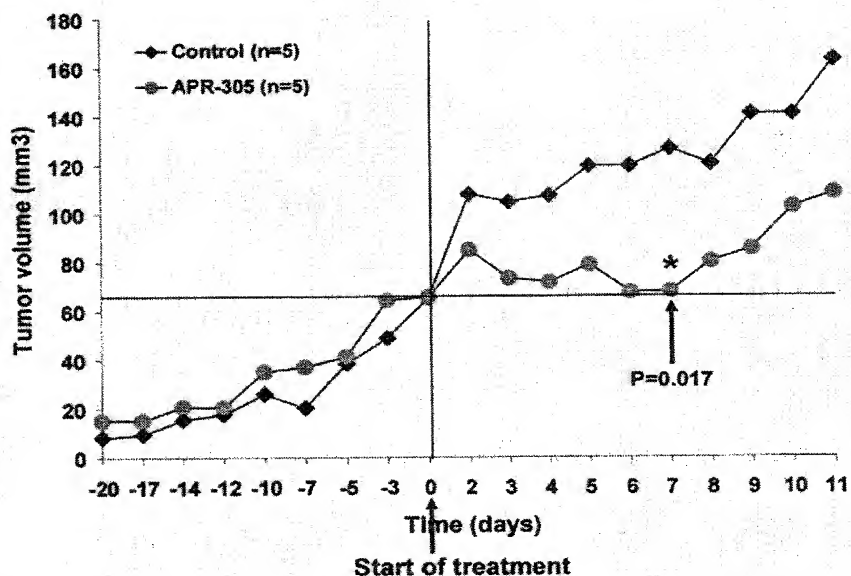
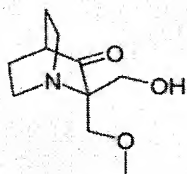
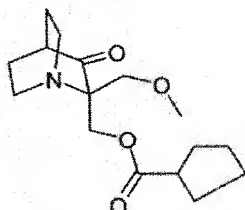


Figure 7. Effect of APR-305, 200 mg/kg, oral administration, on SaOS-2-His273 xenograft tumors in SCID mice. Difference in tumor volume growth was analyzed using two tailed unpaired t-test, unequal variance.

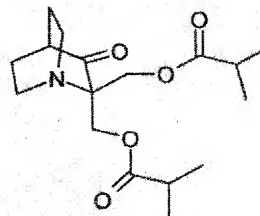
The representative compounds of the invention referred to herein above are as follows:



APR-246



APR-305



APR-310

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The experiments involved and reported above were routine, and they demonstrate pharmacological activity and diseases which would benefit from such activity.

I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

By Nina Mohell
Professor Nina Mohell, PhD

Date: 12-12-08

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The compounds of the invention have been studied in various experiments, both *in vitro* and *in vivo*, with promising results.

In vitro studies

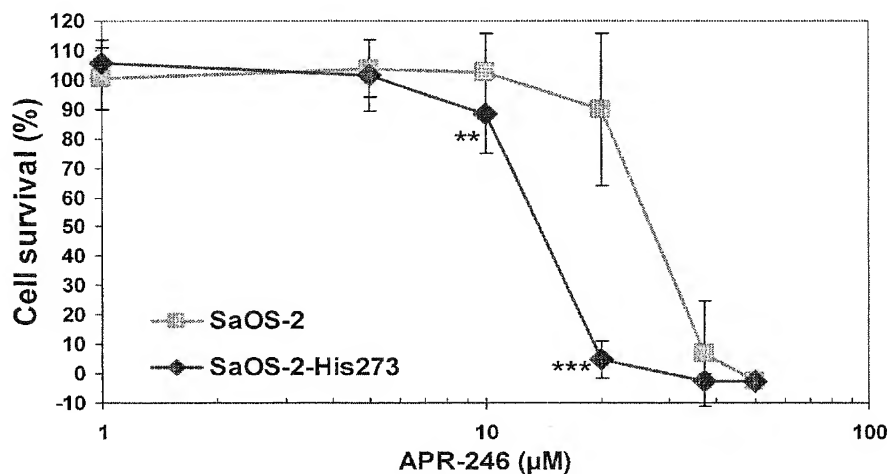
In vitro studies indicate that the inventive compounds have a pronounced inhibitory effect on cancer cell survival and that the activity pattern of the inventive compounds is different from that of many common chemotherapeutic drugs.

1. The inventive compounds inhibit cell viability in osteosarcoma cells

In vitro studies demonstrated that compounds of the invention potentially inhibit cell viability and induce apoptosis in osteosarcoma cells with mutant p53 (SaOS-2-His273) as well as in null p53 (SaOS-2) osteosarcoma cells, being more potent in osteosarcoma cells with mutant p53. Results in respect of two representative compounds of the invention, APR-246 and APR-305 are shown in Figs.1 (APR-246) and 2 (APR-305).

Fig 1.

A



B

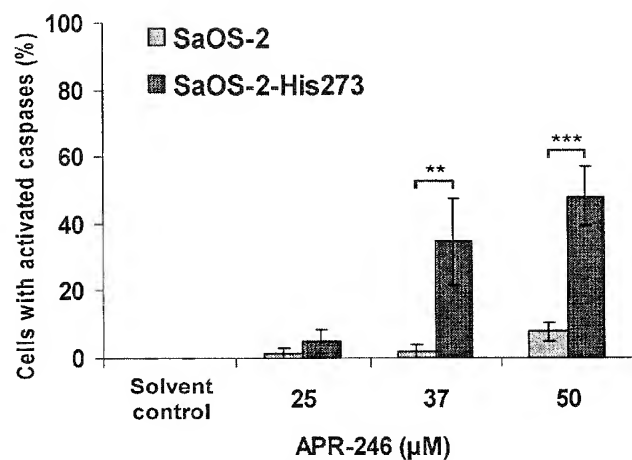
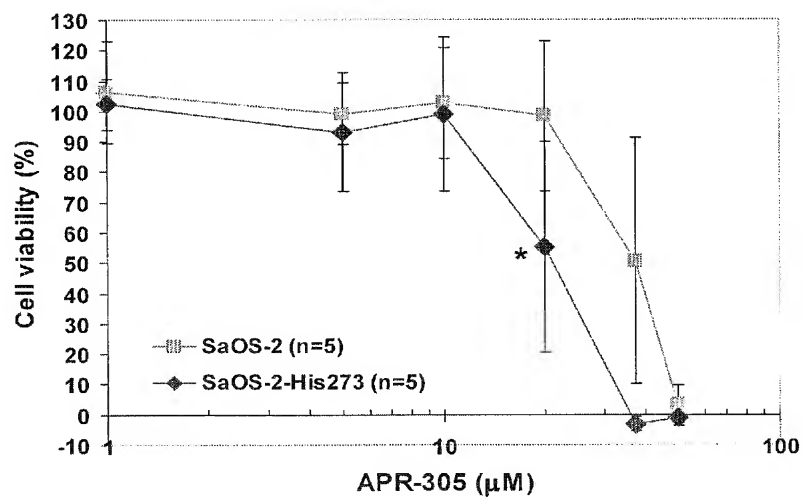


Figure 1. A) Dose-response inhibition curves of APR-246 in SaOS-2 and SaOS-2-His273 cells. Various concentrations of APR-246 were tested in WST-1 proliferation/viability assay. The IC_{50} of APR-246 was 14.5 μ M in SaOS-2-His273 cells and 28 μ M in SaOS-2 cells (mean \pm SD, n=16). **B)** Effect of APR-246 on apoptosis induction in SaOS-2 and SaOS-2-His273 cells. Various concentrations of APR-246 were tested in FLICA apoptosis assay (mean \pm SD, n=5).

Fig 2.

A



B

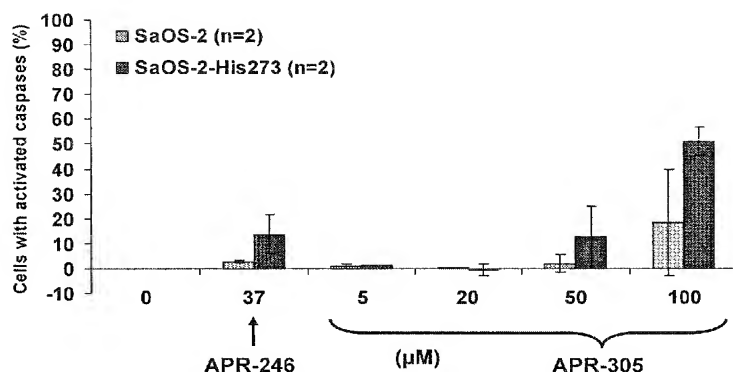


Figure 2. A) Dose-response inhibition curves of APR-305 in SaOS-2 and SaOS-2-His273 cells. Various concentrations of APR-305 were tested in WST-1 proliferation/viability assay. The IC_{50} of APR-305 was 22 μ M in SaOS-2-His273 cells and 38 μ M in SaOS-2 cells (mean \pm SD, n=5). **B)** Effect of APR-305 on apoptosis induction in SaOS-2 and SaOS-2-His273 cells. Various concentrations of APR-305 were tested in FLICA apoptosis assay (mean \pm SD, n=2). APR-246 was used as a positive control.

2. The inventive compounds reduce cell viability in various cancer cell lines with different p53 status

Compounds of the invention were further tested *in vitro* in various cancer cell lines of different p53 status. For each cell line the IC_{50} value was calculated. It was found that compounds of the invention reduce cell viability in various cancer cell lines of different p53 status. In **Table 1**, results for one representative compound of the invention, viz. APR-246, are shown, and in **Table 2** results for three representative compounds of the invention, viz. APR-246, APR-305 and APR-310, in various cancer cell lines are shown. All compounds reduced cell viability in various cancer cell lines with different p53 status.

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Breast adenocarcinoma	MDA-MB-231	mut Lys280	18±5 (n=6)
Prostate adenocarcinoma	PC3-puro	null	27±3 (n=3)
Prostate adenocarcinoma	PC3-175	mut His175 (exogenous)	23±7 (n=3)
Prostate carcinoma	22Rv1	mut Gln331	10±0.6 (n=3)
Colorectal adenocarcinoma	HT-29	mut His273	25±5 (n=6)
Non-small cell lung carcinoma	H1299	null	16±7 (n=6)
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The results are shown as mean±SD; the IC₅₀ values are calculated as the average of the IC₅₀ values in the individual experiments

¹)Mutation is endogenous if not otherwise stated

Table 2. Effect of APR-246, APR-305 and APR-310 on cell viability in various cancer cell lines (WST-1 assay).

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SaOS-2 (p53 null) and SaOS-2-His273 are osteosarcoma cell lines, and KBM3 is an acute myelomonocytic leukemia cell line with a His273 p53 mutation.

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NCI-H69	Small cell lung cancer	-		2,2	7,5	6,6
H69AR	"	doxorubicin	MRP	21	48	40
RPMI 8226/S	Myeloma	-		14	44	42
8226/dox40	"	doxorubicin	Pgp	8,8	40	28
8226/LR5	"	melfalan	glutathione	43	68	44
U-937 GTB	Lymphoma	-		2,4	9,2	7,6
U-937-vcf	"	vincristin	tubulin	5,9	11	8,8

The inhibitory activity of the inventive compounds in the ten cell lines differed from that of many common chemotherapeutic drugs as shown by low correlation coefficients (<0.4), listed in Table 4. Thus, the inventive compounds seem to have an activity pattern showing a unique profile.

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Reference drug	APR 246	APR 305	APR 310
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Cytarabine	0,29	0,19	0,22
Topotecan	0,36	0,30	0,32
Vincristin	0,13	0,08	0,03

In vivo studies

Compounds of the invention have been studied not only *in vitro*, but also *in vivo*. Also the *in vivo* studies show that the inventive compounds have a pronounced anti-cancer activity in the following *in vivo* cancer models:

1. *In vivo* xenograft experiments in mice show that the inventive compounds have a significant anti-cancer effect

A statistically significant anti-cancer effect in *in vivo* xenograft experiments with mutant p53 osteosarcoma cells SaOS-2-His273 (Fig. 3) has been shown for compounds of the invention.

Figure 3 shows the volume of p53 mutant xenograft tumors in SCID mice, treated intravenously with APR-246 or with PBS (the vehicle, control), at a dosage of 100 mg/kg, twice a day, 3-4 days/week. As can be seen, at the end of the treatment period, the mean tumor volume in control animals was more than three times as high as that in animals treated with

APR-246. Differences in tumor volumes were analyzed using Mann-Whitney test. A statistically significant anti-cancer effect was found.

Fig 3.

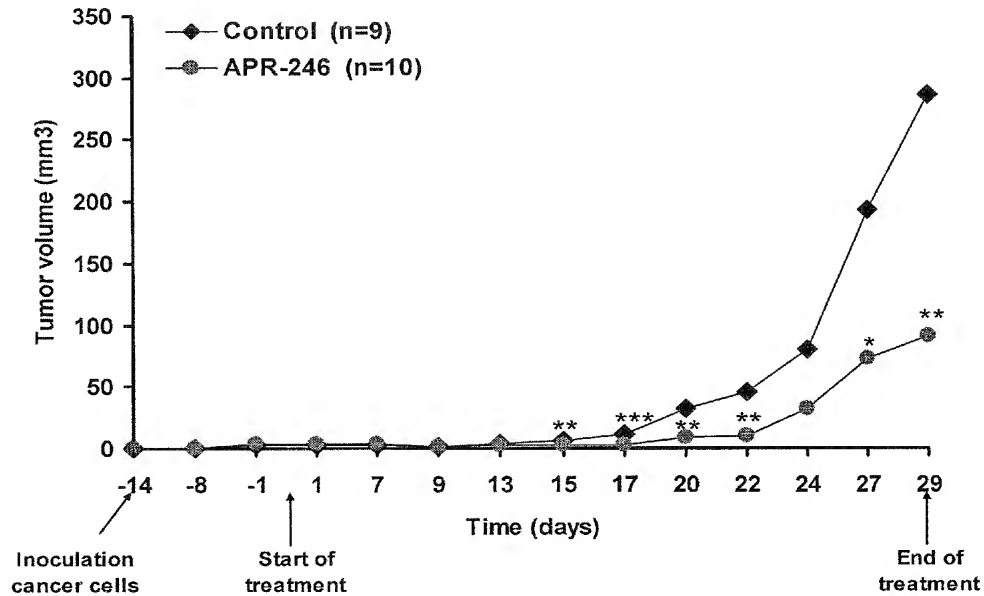


Figure 3. Effect of APR-246, 100 mg/kg, on SaOS-2-His273 xenograft tumors in SCID mice.

2. *In vivo* experiments with mouse tumors carrying mutant p53 show that the inventive compounds have a significant anti-cancer effect

The effect of APR-246 *in vivo* has also been studied by the research group of Klas Wiman (one of the inventors) in experiments using a mouse sarcoma model (**Figure 4**) and a chemically induced fibrosarcoma model (**Figure 5**). In these models APR-246 showed a statistically significant anti-tumor effect. The results provide additional support for an anti-tumor effect of APR-246 on mutant p53 tumors *in vivo*.

Fig 4.

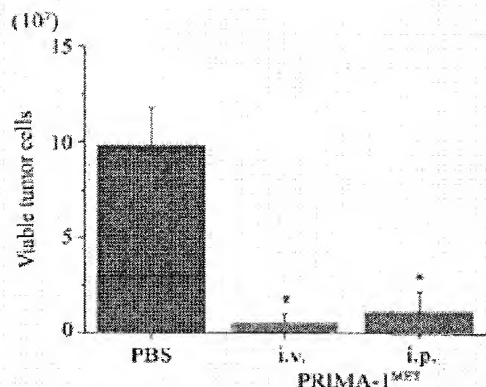


Figure 4. Effect of i.v. or i.p. treatment of APR 246 (PRIMA-1^{MET}), 100 mg/kg, daily, for 10 days, on MC1M mouse sarcoma cells grown as ascites tumors in syngeneic C3H/Hen mice (Zache et al., Cell Oncol. 2008;30(5):411-8). The MC1M cells inoculated in this experiment carry a V213M mutant p53.

Fig 5.

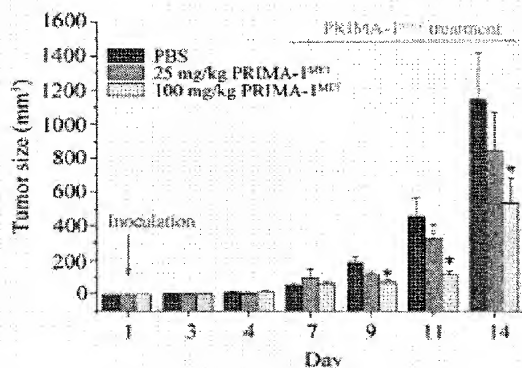


Figure 5. Effect of i.v. treatment of APR 246 (PRIMA-1^{MET}), 25 mg/kg or 100 mg/kg, daily, for 10 days, on MCO4 cells grown as solid subcutaneous tumors in syngeneic Balb/c mice (Zache et al., Cell Oncol. 2008;30(5):411-8). The MCO4 cell line is derived from a 3-methylcholanthrene-induced mouse fibrosarcoma. The cells express two mutant p53 species, one carrying the G65R and R277I mutations and one carrying the R246L mutation.

3. *In vivo* experiments using the hollow fiber mouse model with inventive compounds show that inventive compounds have a significant anti-leukemic effect

Experiments have also been performed with APR-246 at Visionar Preclinical AB using the hollow fiber *in vivo* mouse model (for a short description of the model, cf. http://dtp.nci.nih.gov/timeline/noflash/milestones/M13_hollow_fiber.htm). As shown in **Figure 6**, at the end of the experiment the net growth of leukemic cells (AML MV-4-11 cells) was about 25% (by number) in mice treated with vehicle only (control). On the other hand, in mice treated with APR-246, the net growth of leukemic cells was about -25% by the end of

the experiment, i.e. the number of leukemic cells had effectively decreased. Thus, it was shown that APR-246 has a statistically significant anti-leukemic activity *in vivo*.

Fig 6.

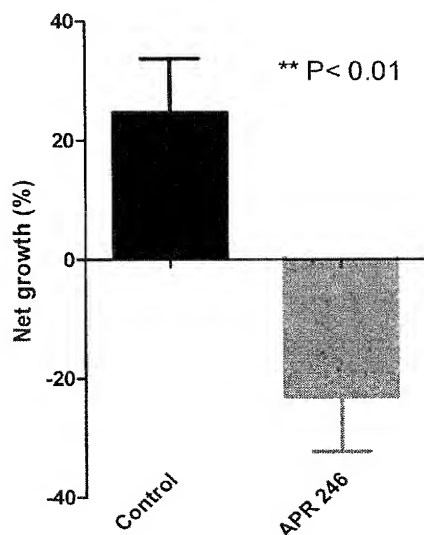


Figure 6. Effect of APR-246 on AML MV-4-11 cells in the hollow fiber *in vivo* model. Data is shown as mean \pm SEM (n=7-8).

4. *In vivo* xenograft experiments with oral administration of inventive compounds to mice show that inventive compounds have a significant anti-cancer effect

Experiments with oral administration of compounds of the invention to SCID mice inoculated with xenografts of p53 osteosarcoma cells have also been performed, with very promising results. **Figure 7** illustrates the effect on SaOS-2-His273 xenograft tumors in SCID mice of oral administration of a representative compound of the invention, viz. APR-305, at a dosage of 200 mg/kg, twice a day, 7 days. The difference in tumor volume growth was analyzed using two tailed unpaired t-test, unequal variance. A statistically significant anti-cancer effect was found.

Fig 7.

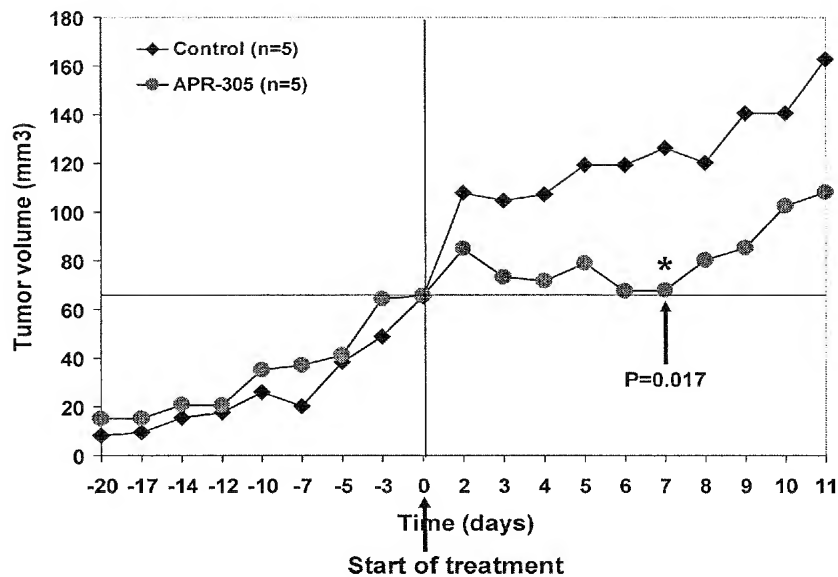
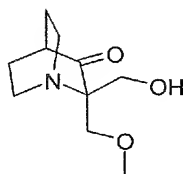
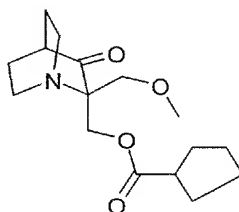


Figure 7. Effect of APR-305, 200 mg/kg, oral administration, on SaOS-2-His273 xenograft tumors in SCID mice. Difference in tumor volume growth was analyzed using two tailed unpaired t-test, unequal variance.

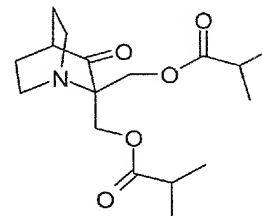
The representative compounds of the invention referred to herein above are as follows:



APR-246



APR-305



APR-310

CV of Nina Mohell

I, Dr. Nina Mohell was awarded the degree of Ph.D. in animal physiology from the University of Stockholm, Sweden in 1985. Three years later I became docent (associate professor), and in 2000, I was appointed as professor (adjunct) in molecular pharmacology at the Faculty of Medicine, University of Uppsala, Sweden.

From 1990 until now (2008) I have been working with various pharmaceutical and biotech companies as follows:

- Astra Arcus AB / AstraZeneca, Södertälje, Sweden (1990-2001)
- Acadia-Pharmaceuticals, San Diego, California (2001-2003)
- Biovitrum AB, Stockholm, Sweden (2003-2004)
- Aprea AB, Stockholm, Sweden (2005-present)

In these companies I have had leading positions as a director of various departments in R&D unit, including neuropharmacology, molecular pharmacology and lead discovery/generation. Thus, I have 18 years of experience of pharmaceutical drug discovery and development with various indication areas including, CNS (central nervous system) metabolic diseases and cancer.

I have totally 67 publications of which 51 in international journals with referee system and 16 reviews or book chapters.

From 2005 to the present I have been employed at Aprea AB as Director of Biology. Therefore, I have participated in and/or led various projects dealing with the compounds and findings in the present application.